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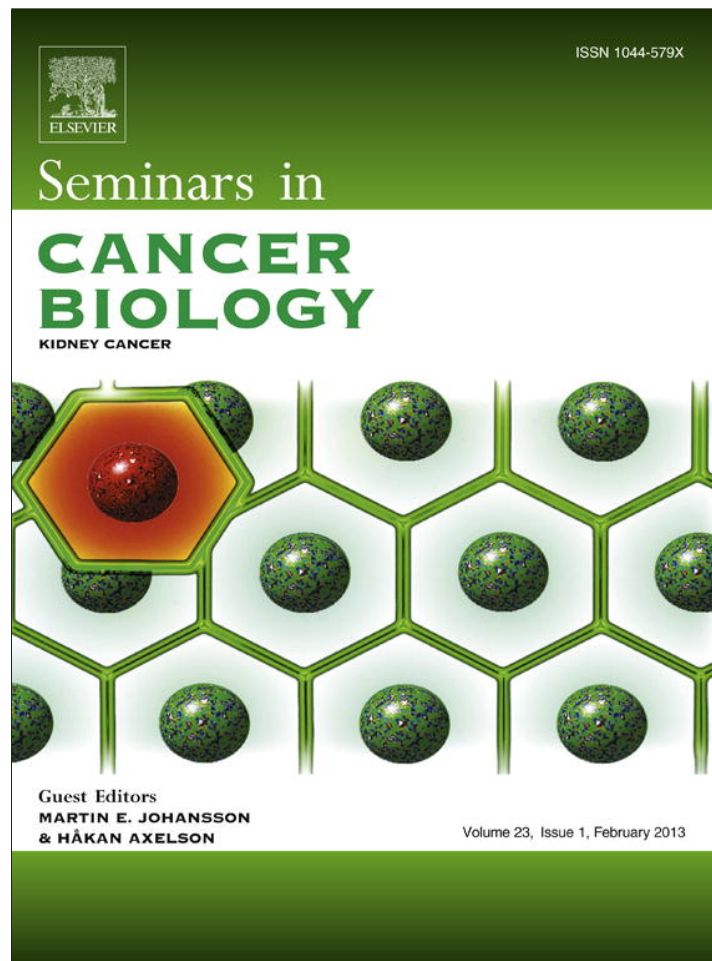
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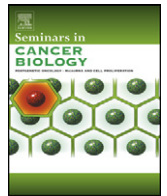


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Review

An overview of renal cell cancer: Pathology and genetics

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ABSTRACT

Renal cell carcinoma is a group of malignancies arising from the epithelium of the renal tubules. The pattern of somatic mutations in kidney tumors has been extensively investigated. In the current 2004 WHO classification, the molecular background of a renal tumor has become, in addition to histopathology, a major criterion for tumor classification. The goal of this review is to discuss morphology and genetics of adult renal epithelial cancer included in the 2004 WHO classification and to mention renal tumor types, which are not considered in the current WHO classification. Further, pathologic considerations with clinical and prognostic implications are provided.

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1. The WHO classification of renal cancer

The term renal cell cancer refers to a heterogeneous group of cancers derived from renal tubular cells. In the last years, pathological and basic cancer research has characterized different renal tumor entities [1,2]. The current WHO renal cancer classification from 2004 combines morphological and genetic characteristics and recognizes some variations of renal cancers with different immunophenotypes or molecular changes with clinical implications [3] (Table 1). These tumor subtypes have different prognosis [4,5] and the response to novel therapies maybe different [6].

Clear cell renal carcinoma is the most frequent renal tumor subtype [7]. These tumors have a very vascular tumor stroma, frequently resulting in hemorrhagic areas. The typical yellow tumor surface is due to the lipid content of the cells; cholesterol, neutral lipids and phospholipids are also abundant (Figs. 1 and 2). Some clear cell renal cell carcinomas have a cystic appearance. This may be due to the presence of necrosis (pseudo-cysts). Presence of tumor necrosis is associated with increased aggressive behavior of the tumors. Some clear cell renal cancer form genuine neoplastic cysts. Cases with complete cystic appearance and without a solid tumoral component are defined as *multilocular cystic renal cell carcinoma* [8]. This subtype has an excellent prognosis and is regarded a low-malignant carcinoma subtype of clear cell renal cancer. Sarcomatoid changes can also occur in clear cell renal carcinoma and is associated with poor prognosis [5,9]. Most renal cell carcinomas have little inflammatory response, but sometimes an intense lymphocytic or neutrophilic infiltrate with natural killer cells is present [10] and there is an association between a strong lymphocytic infiltration and worse outcome [11]. Clear cell renal cell carcinomas

most commonly metastasize hematogeneously via the vena cava primarily to the lung. Retrograde metastasis along the paravertebral veins, the vena testicularis/vena ovarii, intra-renal veins or along the ureter may also be a route of metastasis. Clear cell renal cell carcinoma is well known for its metastasis to unusual sites and late metastasis, even after 10 years or more. All clear cell kidney tumors are considered malignant tumors, independent of the tumor size [3].

Papillary renal cell carcinomas comprise approximately 10% of renal cell carcinoma [5,12,13]. The age distribution of papillary renal cell carcinoma is similar to clear cell renal cell carcinoma with reported mean age at presentation ranging from 50 to 65 years [14]. Papillary renal cell carcinomas frequently contain necrosis. In some tumors, a pseudo-capsule is identified. Bilateral and multifocal tumors are more common in papillary renal cell carcinoma than in other renal malignancies. The histology is characterized by epithelial cells forming papillae and tubules (Fig. 3). The tumor papillae contain a delicate fibro-vascular core. Aggregates of macrophages are frequently present. Psammoma bodies are common. Two morphological types of papillary renal cell carcinomas have been described [15]. Type 1 tumors with papillae covered by small cells with scanty cytoplasm (Fig. 3A). Type 2 tumor cells are often of higher nuclear grade with eosinophilic cytoplasm and pseudo-stratified nuclei (Fig. 3B). Type 1 tumors are more frequently multifocal. Sarcomatoid differentiation is also seen in papillary renal cell carcinoma and is associated with poor prognosis. Papillary renal cell carcinomas entirely composed by oncocytes have been described [16]. This subset of papillary tumors shows clinical-pathologic features different from type 1 and type 2 papillary renal cell carcinomas and has been proposed as a third group of papillary renal tumors.

Chromophobe renal cell carcinoma accounts for approximately 5% of renal cancer. They have a better prognosis than clear cell renal cancer [17,18]. Mortality is less than 10%. Rarely, sarcomatoid

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Fig. 1. Gross appearance of clear cell renal cancer. Bright yellow color in some areas is due to lipid and cholesterol content of tumor cells.

transformation does occur and is a diagnostic sign of poor prognosis [19]. Cases of chromophobe renal cancer have documented distant metastasis into lung, liver and pancreas. It has been suggested that liver metastasis is more frequent in chromophobe renal

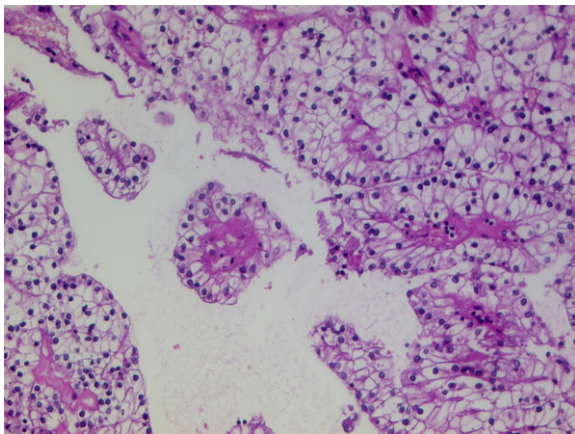


Fig. 2. Microscopic appearance of clear cell renal cancer with classic pattern resembling vegetable cells.

Table 1
WHO histological classification of RCC.

Clear cell renal cell carcinoma
Multilocular clear cell renal cell carcinoma
Papillary renal cell carcinoma
Chromophobe renal cell carcinoma
Carcinoma of the collecting ducts of Bellini
Renal medullary carcinoma
Xp11 translocation carcinomas
Carcinoma associated with neuroblastoma
Mucinous tubular and spindle cell carcinoma
Renal cell carcinoma, unclassified

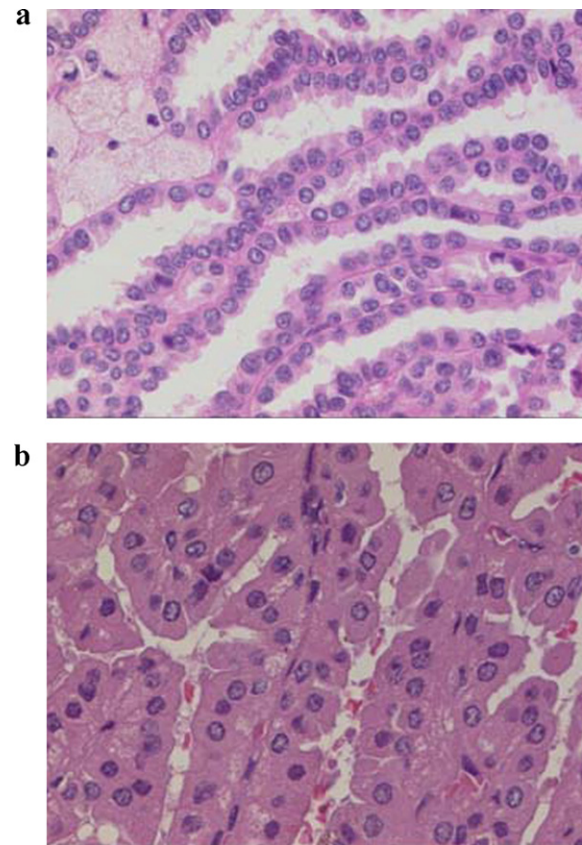


Fig. 3. (A) Papillary renal cell cancer type 1. Tumor cells are relatively small and cuboidal. There are some foam cells. (B) Papillary renal cell cancer type 2. Tumor cells are larger with eosinophilic cytoplasm.

cancers than in other histological subtypes [20]. The cut surface of chromophobe renal cell carcinoma appears homogeneously gray or gray-brown (Fig. 4). The tumor is characterized by large polygonal cells with reticulated cytoplasm and prominent cell membranes. Some cells are irregular and multinucleated. Perinuclear halos are common. A diagnostic hallmark is a diffuse cytoplasmic staining reaction with haes colloidal iron staining [21]. The eosinophilic variant of chromophobe renal carcinoma is purely composed of eosinophilic cells. Electron microscopically, the cytoplasm is characterized by glycogen deposits and numerous vesicles. The major differential diagnosis of chromophobe renal carcinoma is renal oncocytoma. *Renal oncocytoma* is considered to be a benign neoplasm [22]. It has been postulated that eosinophilic chromophobe renal cell cancer originates from renal oncocytoma, and represents the malignant form of this tumor. However, this hypothesis has not been proven. The so-called hybrid tumors share histopathological characteristics of chromophobe carcinoma and oncocytoma.

Collecting duct carcinoma is a very rare subtype of renal cell carcinoma, accounting for about 1% of all renal cancer types. This tumor type is extremely aggressive with frequent metastasis already at presentation [23–25]. These tumors are usually located in the central region of the kidney and have a gray-white appearance with irregular borders. They often display infiltration of peri-renal and renal sinus fat. Metastasis to regional lymph nodes, lung, liver, bone and adrenal glands are comment. Histologically, collecting duct cancer is characterized by a tubulo-papillary architecture with a characteristic desmoplastic stroma reaction. *Renal medullary carcinoma* is a rapidly growing tumor of the renal medulla associated almost exclusively with sickle cell trait. This is an extremely rare tumor. The majority of cases show sickled erythrocytes [26,27].

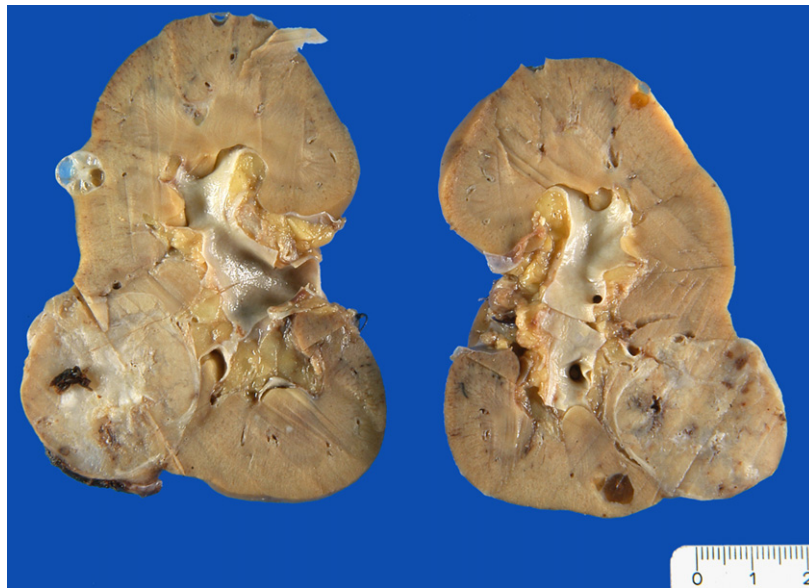


Fig. 4. Gross appearance of chromophobe renal cancer. The tumor is well circumscribed and has a gray color.

Translocation carcinomas associated with Xp11.2 translocations/TFE3 gene fusions are characterized by different translocations involving chromosome Xp11.2, resulting in gene fusions involving the *TFE3* gene. Meanwhile, different fusions are identified, including the t(X;1)(p11.2; q21) fusion, the t(X; 17)(p11.2;q25), which results in fusion of the *ASPL* and *TFE3* genes and the t(X;1)(p11.2;q34), resulting in fusion of the *PSF* and *TFE3* genes as well as other fusions [28–31]. Translocation carcinomas predominantly affect children and young adults [32]. However, translocation carcinomas also occur in older patients [33]. Histologically, translocation carcinomas have a papillary architecture comprised of clear cells with voluminous clear to eosinophilic cytoplasm. Psammoma bodies can be present. The immunoprofile is characterized by nuclear immunoreactivity for TFE3 protein. Only 50% express epithelial markers such as cytokeratin and EMA by immunohistochemistry. In adults, translocation carcinomas are associated with poor prognosis, presenting at advanced stages, frequently with lymph node metastasis at diagnosis.

Renal cell carcinoma after neuroblastoma are seen in long term survivors of childhood neuroblastoma [34]. Therefore it has been suggested that therapy for neuroblastoma plays a role in the pathogenesis of these renal carcinomas. These tumors are

morphologically heterogeneous with solid and papillary architecture and cells with eosinophilic cytoplasm.

Mucinous tubular and spindle cell carcinomas are low-grade renal epithelial neoplasms with tubular and spindle cell features and mucinous stroma [35,36]. They usually present as asymptomatic masses. The prognosis is favorable in most cases (Fig. 5).

Renal cell carcinoma, unclassified is a term for a renal cancer case, which is not defined in the current WHO classification. This group represents less than 5% of all renal cell carcinomas. Most of these cases have sarcomatoid morphology without recognizable epithelial elements, mucin production or unrecognizable cell types [37]. Since there is no evidence that renal tumors arise de novo as sarcomatoid carcinomas, this type is not viewed as a type of its own. Most unclassified RCC are associated with a highly aggressive biological behavior and poor clinical outcome.

2. Renal cancer subtypes – not yet considered in the WHO classification

Tubulocystic carcinomas are tumors composed by tubules and cysts lined by cuboidal or hobnail cells with eosinophilic cytoplasm and large nuclei showing prominent nucleoli [38]. These tumors have a characteristic macroscopy with a white or a gray spongy cut surface. Most of these cases are early stage tumors. The histogenesis of tubulocystic carcinoma may represent a subset of papillary renal cell carcinoma or collecting duct cancer. Due to their specific pathological images, this type of RCC should be included as a distinct tumor entity in a future WHO classification.

Thyroid-like renal carcinoma is a renal carcinoma with a follicular architecture resembling follicular carcinoma of the thyroid [39]. The tumors are composed of cells showing low-grade pleomorphism with eosinophilic cytoplasm. Metastasis from a primary thyroid follicular carcinoma has to be excluded and TTF1 expression as a marker of thyroid carcinoma should always be undertaken in tumors showing this morphology to exclude metastatic disease.

Acquired cystic disease-associated renal cell carcinomas are tumors associated with end-stage renal disease. In end-stage renal disease, all renal cancer subtypes are found [40]. Specific subtypes include acquired cystic disease-associated renal cancer with presence of oxalate crystals and large eosinophilic cells with rounded

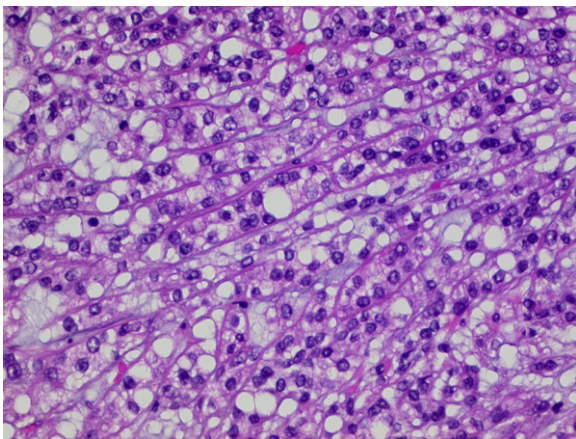


Fig. 5. Typical microscopic appearance of mucinous tubular and spindle cell carcinoma showing low-grade spindle cell areas and stromal mucin.

nucleus and large nucleolus. The second type is the clear cell papillary renal carcinoma. This tumor is characterized by cells with clear cytoplasm and low-grade nuclear pleomorphism, frequently with a dominant cystic component. Clear cell papillary RCC frequently contain a prominent pseudocapsule. This type can also be seen in kidneys both with or without acquired cystic disease and is characterized by a good prognosis [37].

Leiomyomatous renal cell carcinomas are composed of tubular aggregates of neoplastic clear cells intermixed with a prominent leiomyomatous proliferation [37]. The smooth muscle component is often more pronounced at the periphery. There is currently a debate regarding the relationship between clear cell papillary RCC and leiomyomatous renal cell carcinoma. A relationship to clear cell renal cancer appears possible. Clear cell papillary renal cell carcinoma may also show overlapping morphological features to leiomyomatous renal cell carcinoma. Therefore, a formal classification is early.

3. Hereditary renal cell carcinoma

Almost all renal cell tumor types occur in a sporadic or in a hereditary form [41]. Usually, affected patients develop bilateral or multiple renal tumors. Within the last years, a number of hereditary tumor syndromes with predisposition to the development of renal cell carcinoma have been identified. The molecular analysis of tumor tissue in mutation carriers with renal and extrarenal neoplastic manifestations has led to the identification of the predisposing genes. These genes include *VHL*, *MET*, *FH*, *BHD* and *HRPT2* (Table 2). The hereditary renal cell carcinoma syndromes are extremely rare. *VHL* disease is the most frequent familial renal cancer syndrome and is associated with clear cell renal carcinoma, escorted by mutations in the *VHL* gene and loss of the wild-type *VHL* (see Section 3) [42]. Patients with hereditary papillary renal cell carcinoma syndrome have multiple, bilateral papillary renal cell carcinomas with papillary type 1 histology. The patients have a germ line activating mutation in the *MET* proto-oncogene [43,44].

Papillary type-2 renal carcinomas and uterine smooth muscle tumors are associated with hereditary leiomyomatosis and renal cell cancer syndromes (HLRCC), which is caused by germ line loss-of-function mutations in the fumarate hydratase (*FH*) gene. The hyperparathyroidism-jaw tumor (HPT-JT) syndrome is associated with parathyroid adenomas, fibro-myalgic tumors of the jaw and renal tumors. This syndrome is caused by germ line mutations in the *HRPT2* gene [45,46]. The Birt-Hogg-Dubé (BHD) syndrome is associated with an increased risk for renal cancers, especially for chromophobe renal cell carcinomas and oncocytomas [47,48]. In some cases, so-called oncocystic hybrid tumors are seen. Tumors can be multiple and bilateral. The skin tumors include fibrofolliculomas, trichodiscomas and acrochordomas. Spontaneous pneumothorax and the presence of pulmonary cysts are recognized features of the BHD syndrome. The *BHD* gene maps to chromosome 17p11.2. Multiple, unilateral or bilateral clear cell renal cell carcinomas are found in the constitutional translocation of chromosome 3. Affected family members carry a balanced chromosome translocation, involving chromosome 3.

4. Cytogenetic and molecular alterations in renal cell carcinomas subtypes

The pattern of somatic mutations in kidney tumors has been extensively investigated and has become a major criterion for classification [1]. Chromosome 3p deletion (LOH 3p) is the most typical genetic abnormality in sporadic clear cell renal cell carcinoma and is regarded as an important step in tumor initiation. Different genes have been located on the short arm of chromosome 3 which are

probably involved in renal carcinoma. One of them is the von Hippel-Lindau disease tumor suppressor gene in 3p25-26 [49,50]. Other putative genes at 3p are *PBRM1* [51], *RASSF1a* [52] and *NRC-1* [53]. The consequences of the mutations of the *VHL* gene are discussed in Sections 3 and 6. Recently, mutations of the *VHL* gene have been reported in multilocular cystic renal cell carcinoma and confirm the hypothesis that multilocular cystic renal cell carcinoma represent a subtype of clear cell renal cancer [54]. The relationship of leiomyomatous renal cell carcinoma and clear cell papillary renal cancer based on the presence or absence of *VHL* mutation and/or 3p losses is currently controversial. Apart from the *VHL* inactivation as an initiating event in clear cell renal cancer, many different genetic alterations have been reported for this tumor type, some of them associated with prognosis [55–67].

Papillary renal cell carcinoma is characterized by trisomy/polysomy of chromosomes 3q, 7, 8, 12, 16, 17 and 20 and loss of the Y-chromosome [68,69]. The *c-met* proto-oncogene mutation on chromosome 7 characterizes hereditary papillary renal cell carcinomas but is rare in sporadic papillary renal cell carcinoma [44,43].

Karyotyping, fluorescence and in situ hybridization and comparative genomic hybridization revealed that multiple and non-random chromosomal losses of chromosomes 1, 2, 6, 10, 13, 17, 21 and the Y or X chromosomes are frequent in chromophobe renal cancer, whereas renal oncocytomas have only rearrangements or translocations involving 11q13 or partial losses of chromosomes 1, 14 and sex chromosomes [70]. In contrast, loss of the short arm of the chromosome 3 is rare [71]. In collecting duct cancer, trisomy/polysomy for chromosomes 4, 7, 8, 17 and 20 and loss of chromosomes 14, 18 and 22 were reported [72]. Also, loss of other chromosomes has been described. In mucinous tubular and spindle cell carcinoma, losses involving chromosomes 1, 4, 6, 8, 13, 14 and 15 and gains of most other chromosomes have been reported [73]. However, most of these tumors also show the gains of chromosome 7 and 17 that are typically found in papillary renal cell carcinomas. As mentioned above, translocation carcinomas are defined by Xp11.2 translocations resulting in TFE3 gene fusions. Gene expression profiling and fluorescence in situ hybridizations studies indicate that tubulocystic carcinomas have gains of chromosome 7 and 17, supporting the hypothesis that these tumors represent a subset of papillary renal cell carcinoma [38,74,75]. In thyroid-like renal cell carcinomas a widespread under- or over-expression of genes, particularly involving chromosomes 1, 2, 3, 5, 6, 10, 11, 16 and 17 is present [39]. In acquired cystic disease-associated RCC's, multiple gains of numerous chromosomes, including chromosomes 1, 2, 6, 10, 3, 7, 17 and Y were seen [76]. Mutations of the *VHL* gene have not yet been identified in these tumors. Clear cell papillary RCC did not show 3p losses or trisomy of chromosome 7 and 17. Therefore, the potential relationship of these tumors to other tumor entities is unclear. Genetic studies on leiomyomatous renal cell carcinomas are controversial. In some cases, loss of chromosome 3 has been reported. In other studies, there was no evidence of 3p deletion in the 3 cases examined [37].

5. The cell of origin in renal cell cancer?

Renal cancer a heterogeneous tumors, which may be derived from specific cells within the nephron and collecting ducts. Based on older immunohistochemical analyses, it has been suggested that clear cell and papillary renal cell carcinomas are derived from the proximal tubules [77], chromophobe renal cancer and oncocytoma from the distal nephron [17] and collecting duct cancer from the ducts of Bellini [17,78–80]. It was tempting to speculate that mucinous tubular and spindle cell carcinoma are derived from the loop of Henle [73], and tubulocystic carcinoma also from the collecting

Table 2
Hereditary renal cell tumors.

Syndrome	Chr.	Gene	Protein	Tumor type	Extrarenal manifestations	
					Dermis	Other organs
von Hippel–Lindau	3p25	<i>VHL</i>	pVHL	Multiple, bilateral clear cell RCC, renal cysts	–	Hemangioblastoma of retina/cns; pheochromocytoma; pancreatic-/renal cysts; neuroendocrine tumors; epididymal/parametrial cysts; tumors of the inner ear
Hereditary papillary RCC	7p31	<i>c-MET</i>	HGF-R	Multiple, bilateral papillary RCC (type 1)	–	–
HLRC	1q42	<i>FH</i>	FH	Papillary RCC (non-type 1)	Leiomyoma	Uterine leiomyoma/leiomyosarcoma
Familial papillary thyroid carcinoma	1q21	?	?	Papillary RCC oncocytomas	–	Papillary thyroid carcinoma
Hyperpara – thyroidism – jaw tumor syndrome (HP-JT)	1q25	<i>HRPT2</i>		Epithelial–stromal mixed tumors, papillary RCC	–	Tumors of the parathyroidea; fibro-osseous jaw tumors
Birt–Hogg–Dubé	17p11	<i>BHD</i>	Folliculin	Multiple chromophobe RCC, oncocytoma, papillary RCC	Facial fibrofolliculoma	Pulmonal cysts; spontaneous pneumothorax
Tuberous Sclerosis	9q34 16p13	<i>TSC 1</i> <i>TSC 2</i>	Hamartin Tubertin	Multiple, bilateral angiomyolipomas, lymphangioliomyomatosis; Rare clear cell RCC	Angio-fibroma: subungual fibroma	Cardiac rhabdomyoma; adenomatous small intestine polyps; pulmonal/renal cysts; cortical tuber; subependymal giant cell astrocytomas
Constitutional translocation chr.3	3p13–14	?	?	Multiple, bilateral clear cell RCC	–	–

tubules or proximal tubules. However, this model is recently challenged. Mandriota et al. have shown that CA-9 expression, a specific read out for HIF activation can be seen in cells of the proximal as well as distal nephron [81]. CA-9 positive single cells are regarded as precursor legions of clear cell renal cell carcinomas in VHL syndrome. Recently, it has been shown that such CA9-positive cells have VHL-deletions in cystic lesions of patients with VHL-disease [82]. Therefore, a model of a cyst-dependent renal cell carcinoma pathway in VHL disease and a potential cyst-independent progression pathway in sporadic renal cell carcinoma was proposed [83–85]. These progression pathways are potentially independent of the position within the nephron. The relevance of renal stem cells as cell of origin for renal cell carcinoma is discussed in Section 6.

6. Prognosis of renal cell carcinoma and the use of biomarkers

The biological behavior of renal cell carcinoma is unpredictable by histology alone. At the moment, the most accepted prognostic factors are tumor stage and the histological differentiation grade. The correct pathological staging is the basis for every clinical decision [86]. In the last years, it has been demonstrated that invasion of the sinus fat tissue is more frequent than expected and is associated with greater tumor aggressiveness [87–89]. This sinus fat tissue contains a number of large thin-walled veins and lymphatics and it is not separated from the renal cortex by a fibrous capsule.

The most accepted grading system is Fuhrman's grade, which was applied to all renal cancer subtypes [90] and represents the most accepted prognostic parameter. Recently, some criticism appears in the use of Fuhrman grading system in RCC of the non-clear cell types [91]. Fuhrman's grading seems not to be appropriate to grade chromophobe renal cancer and other grading systems have been recently proposed to better predict prognosis of this tumor type [92,93]. In addition, mucinous tubular and spindle cell carcinoma is not graded. Likewise, the oncocytoma is a benign tumor and should not be graded.

In addition to Fuhrman's grade and tumor stage, multiple renal cell biomarkers have been studied in the last years [94]. Molecular events that are involved in renal cancer pathogenesis may

influence the clinical behavior of renal cell carcinoma and may help in improving individualized prognostication and risk-stratified clinical decision making. The molecular dissection of renal cell cancer by gene expression studies has increased our understanding of the pathways that are altered in renal cancer cells, leading to plenty potential renal cancer biomarkers [95,96]. However, there are no useful clinical or pathological biomarkers at the moment, which are routinely used in the prognostication of renal cell carcinoma or in the prediction of the response to novel targeted drugs. Additional biomarker may have some added value when incorporating within existing prognostic models, but the potential for improving the predictive and/or prognostic ability is limited. Most of the molecular biomarkers are associated with other established clinical and/or pathological characteristics of renal cell cancer and are parts of the VHL/HIF-signaling pathway [97–99]. Therefore, the value of novel markers has to be proofed within the framework of existing models [100]. In the future, the probability of response to targeted therapy represents an important field in RCC research.

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